REMARKS

Claims 1, 4, and 7-11 have been amended, claims 19-21 have been added, and claims 2 and 12-18 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the cancelled subject matter in future applications. Claim 1 has been amended to delete the recitation of SEQ ID NO: 4 and to change the numbering within the claim to letters to avoid confusion with claim numbers. Claims 4, 7 and 8 have been amended to correct their dependencies so that they do not depend from cancelled claims. Claim 7 is dependent on claims 1 or 3 and has been further amended to recite "isolated polypeptide" as recited in claims 1 and 3. Thus, no new matter has been added. Claims 8-11 have been added to recite step (a), "introducing into a cell an isolated polynucleotide . . . ." Support for the amendments can be found throughout the specification, for example, page 20, lines 16-23. Therefore, the amendments are fully supported by the specification. Claim 9 has also been amended to recite a selection step (d) that includes "selecting the substance that . . . inhibits leukocyte activation." Support for the amendment can be found throughout the specification, for example, page 9, lines 17-29, and pages 39-42. Therefore, the amendment is fully supported by the specification. New claims 19-21 are also fully supported by the specification, for example, at pages 8-11. Upon entry of the amendments, claims 1, 3-11, and 19-21 are pending.

Applicants address below each issue raised in the Office Action of September 8, 2006.

Priority

The Office indicated that the priority documents JP 2002-225114 (filed August 1, 2002) and JP 2003-182989 (filed June 26, 2003) of the instant application have been received but have not been translated. Applicants have enclosed a certified translation of each of the priority documents.

Claim Objections

The Office objected to claims 1, 2, and 8-11 because they recite subsections (1) and (2) or steps (1) through (3), which would be better expressed as letters, (a), (b), (c), etc., to avoid potential confusion with claim numbers. Applicants have amended the claims to recite letters rather than numbers as suggested by the Office. Withdrawal of the objection is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claim 11 is rejected under 35 U.S.C. § 112, second paragraph, as being allegedly incomplete for omitting a selection step between steps (2) and (3) for the substance to be prepared. Without acquiescing to the rejection, Applicants have added a selection step (d) in claim 11. The amendment is fully supported by the specification at page 9, lines 17-19 and pages 39-42. Therefore, Applicants respectfully request withdrawal of the rejection.

35 U.S.C. § 102

A. Li et al., J. Biol. Chem. 277:48410-48417 (December 2002)

Claims 1-7 and 18 are rejected under 35 U.S.C. § 102(a) as being anticipated by Li et al. The Office asserts that Li et al. teaches an amino acid sequence of NCKX4 that meets the limitation of claims 1 and 2 reciting "a polypeptide in which 1 to 5 amino acids

in total are substituted, deleted, inserted and/or added at one or plural portions . . . of SEQ ID NO: 2."

Applicants respectfully traverse. Li et al. was published on December 2002. As discussed under the "Priority" section above, Applicants have enclosed a certified English translation of each of the priority documents JP 2002-225114 (filed August 1, 2002) and JP 2003-182989 (filed June 26, 2003). The priority documents provide a fully enabling disclosure of the full scope of the claims. In particular, the JP 2002-225114 priority document filed August 1, 2002, discloses, for example, at pages 2 and 5 of the certified English translation, "a polypeptide in which 1 to 5 amino acids in total are substituted, deleted, inserted and/or added at one or plural portions . . . of SEQ ID NO: 2." Consequently, Li et al. cannot be considered prior art against the instant claims. Therefore, Applicants respectfully request withdrawal of the rejection.

B. US Patent No. 6,787,352 (Friddle et al.)

Claims 1 and 3-11 are rejected under 35 U.S.C. § 102(e) as being anticipated by Friddle et al., which was filed on September 24, 2001 and issued on September 7, 2004.

The Office alleges that Friddle's SEQ ID NO: 2 is 100% identical to SEQ ID NO: 4 recited in the instant claims and that the polynucleotide encoding the instantly claimed polypeptide of SEQ ID NO: 4 is also disclosed and claimed by Friddle. The Office further alleges that Friddle teaches expression vectors comprising the polynucleotide and host cells comprising the expression vectors, and production of the polypeptide from these host expression vector systems.

With respect to the method claims, the Office alleges that Friddle discloses methods for identifying compounds that act as agonists or antagonists of the disclosed protein's endogenous activity. While the Office acknowledges that Friddle is silent with respect to whether a substance would inhibit the potassium-dependent sodium-calcium exchange activity of the protein, the Office contends that such a substance would necessarily have that property if identified by the screening assay. The Office alleges that such screening assays would therefore also anticipate the method of claims 9 and 10 because the recited method steps are the same. Moreover, the Office alleges that the production of therapeutic compounds as in instant claim 11 is also anticipated because compounds found by the screening method disclosed by Friddle allegedly are disclosed as being useful as pharmaceutical reagents in therapeutic treatment of mental, biological, or medical disorders and disease.

Applicants respectfully disagree. Without acquiescing to the rejection, claim 1 has been amended to no longer recite SEQ ID NO: 4. Claims 3-8 ultimately depend on claim 1 and therefore, the rejections of claims 1 and 3-8 are rendered moot. Claims 9-11 recite a method for "screening for an inhibitor of leukocyte activation," "screening for a therapeutic agent for postischemic reperfusion injury and/or an inflammatory disease," and "manufacturing a pharmaceutical composition for treating postischemic reperfusion injury and/or an inflammatory disease," respectively. Nowhere does Friddle teach any of these methods. While the Office alleges that Friddle discloses the treatment of mental, biological, or medical disorders and disease with compounds discovered by a screening method, Friddle's disclosure is so broad that it essentially covers treatment of any disorder or disease. The only specific examples Friddle provides are for the

"treatment of cancer, arthritis, or as antiviral agents." (Col. 11, lines 5-7). These cannot anticipate instant claims 9-11.

Furthermore, claim 9 requires a selection step, including the selection of a substance that "inhibits leukocyte activation." Friddle does not teach that its "novel human proteins" (NHPs) are expressed in leukocytes. In fact, Friddle provides a long laundry list of the types of cells and tissues that the NHPs could be expressed but does not mention leukocytes or peripheral blood. (*See* col. 2, lines 37-47). Therefore, Friddle fails to teach inhibition of leukocyte activation as recited in claim 9.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

35 U.S.C. § 103

Claims 8-11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mochizuki and Jiang (*Japanese Heart J.*, 1998, 39:707-714) in view of Harada et al. (*J. Pharm. Exp. Therapy*, 2000, 294:1034-1042) as evidenced by Balasubramanyam et al. (*J. Clin. Invest.*, 1994, 94:2002-2008).

The Office contends that "Mochizuki and Jiang indicate that agents which inhibit the sodium-calcium exchanger may have therapeutic potential for the treatment of ischemia/reperfusion injury." The Office, however, acknowledges that Mochizuki and Jiang do not teach methods to screen for therapeutic agents or for agents capable of inhibiting leukocyte activation. The Office therefore combines Harada et al., which allegedly teaches methods for screening various compounds *in vitro* and *in vivo* for their effectiveness in reducing inflammation and/or injury caused by ischemia/reperfusion. The Office also notes that Balasubramanyam et al. teaches that cytosolic Ca^{2+}

concentration in human leukocytes is regulated by Na^+/Ca^{2+} exchanger activity and therefore, "leukocytes used in such assays would intrinsically possess the polypeptides of the instant invention exhibiting potassium-dependent sodium-calcium exchange activity."

Applicants respectfully disagree. As discussed in the instant specification at page 4, two types of sodium-calcium exchangers exist: 1) the classic potassium-independent sodium-calcium exchanger (NCX) and 2) the potassium-dependent sodium-calcium exchanger (NCKX). The instant application is directed to the latter, potassium-dependent exchanger. *See* specification at page 7, second paragraph under "Disclosure of Invention." However, nothing in Mochizuki and Jiang suggests that it is directed to the potassium-dependent exchanger. The Office directed Applicants to the paragraph bridging pages 712 and 713 of Mochizuki and Jiang where they noted that "[d]irect inhibition of the Na^+/Ca^{++} exchanger or reduction of Na^+/H^+ exchanger activity and cytosolic Na^+ concentration have been shown to protect the myocardium from reperfusion-induced cellular injury." Nothing in this paragraph suggests a potassium-dependent sodium-calcium exchanger. In fact, nothing in references 24, 35, and 36[1] cited by Mochizuki and Jiang to support their statement suggests the involvement of a potassium-dependent exchanger. For example, none of these references tested for potassium-dependence of these sodium-calcium exchangers.

[1] Reference 24 is Murphy et al., *Circulation Research* 58:1250-1258 (1991); reference 35 is Meng et al., *Am. J. Physiol.* 258:H1615-1619 (1990); and reference 36 is Mochizuki et al., *Mol. Cell Biochem.* 119:151-157 (1993).

Significantly, Mochizuki and Jiang do not teach or suggest a polypeptide consisting of SEQ ID NO: 2 or SEQ ID NO: 4. Therefore, Mochizuki and Jiang do not teach or suggest using these polypeptides to identify substances that inhibit their activities. As the Office acknowledged, Mochizuki and Jiang also do not teach methods to screen for therapeutic agents or for agents capable of inhibiting leukocyte activation.

Harada et al. and Balasubramanyam et al. fail to make up for the deficiencies of Mochizuki and Jiang. Harada et al. not only fails to teach or suggest a polypeptide consisting of SEQ ID NO: 2 or SEQ ID NO: 4, it does not even discuss any type of sodium-calcium exchanger. Harada et al. simply suggests reduction of ischemia/reperfusion injury by inhibiting leukocyte activation with adenosine and selective A_{2A} receptor agonists. To the extent that Harada et al. suggests that Ca^{2+} plays an important role in leukocyte activation by neutrophil elastase release, the Office attributes this role of Ca^{2+} to a sodium-calcium exchanger based on the teachings of Balasubramanyam et al. The Office improperly argues that because Balasubramanyam et al. teaches that cytosolic Ca^{2+} in human leukocytes is regulated by Na^{+}/Ca^{2+} exchanger activity, the leukocytes of Harada et al. inherently possessed the polypeptides of the instant invention. However, nothing in Balasubramanyam et al. suggests that a potassium-dependent sodium-calcium exchanger of the claimed invention were expressed in the leukocytes.

Additionally, "[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." *In re Rijckaert*, F.2d 1531 (Fed. Cir. 1993); MPEP § 2141.02(V). The polypeptide of SEQ ID NO:2 was first discovered by the inventors and therefore, there was no

recognition in the art that the polypeptide of SEQ ID NO:2 existed in leukocytes. Similarly, as discussed in relation to the Friddle reference above, there was no recognition in the art that the polypeptide of SEQ ID NO: 4 was expressed in leukocytes.

Even if the leukocytes used by Balasubramanyam et al. intrinsically possessed a polypeptide of SEQ ID NO: 2 or SEQ ID NO: 4, and even if the case law permitted an obviousness rejection to be based on inherency, Balasubramanyam et al. and Harada et al. did not use an isolated polynucleotide to express the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 4. Therefore, the claims cannot be rendered obvious. Applicants respectfully request withdrawal of the rejection.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 29, 2006

By: _____
Yuko Soneoka
Limited Reg. No. L0093